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PERFORMANCE OF METERED DOSE INHALER (MDI) AND SPRAY CHARACTERISTICS

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Bachelor of Engineering with Honours
(Mechanical Engineering and Manufacturing Systems)
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Approval Sheet

This project report attached here to, entitled **"Performance of Metered Dose Inhaler (MDI) and Spray Characteristics"** prepared and submitted by **Rosliana Binti Rusli** as a partial fulfillment of the requirement degree in Bachelor of Engineering with Honors in Mechanical Engineering and Manufacturing System is hereby read and approved by:

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In the name of Allah, the beneficent, the merciful peace and blessing upon His messenger and servant, Muhammad. There is no god but Allah and Muhammad is His Apostle. All praise to be Allah SWT who has given me the guidance and strength to be steadfast in my pursuit of knowledge amidst trials and challenges.

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ABSTRACT

Metered dose inhaler (MDI) has been widely used for treating asthma for more than a century. The understanding of MDI application, and its spray characteristics are therefore essential. The sprayer strengths and weaknesses were reviewed. The review was narrowed down to commonly use hand-held MDI sprayers and thus, leads to recommendation for modification of this type of sprayer. The effects of nozzle designs on the spray characteristics of the sprayer were discussed. The spray characteristics were investigated through qualitative and quantitative studies. Initial experimental results of the spray characteristics, were discussed. The results showed the shape of spray plumes at different time interval. The application of electrical forces, allowing the spray plume to be manipulated for better atomization and droplet deposition in the mouth, which will lead to design of a novel electrostatic medical nasal sprayer, was also discussed.

ABSTRAK

Metered dose inhaler (MDI) telah digunakan secara meluas lebih dari seabad. Pemahaman tentang penggunaan *MDI* dan juga ciri-ciri semburannya adalah penting. Kekuatan dan kelemahan semburan telah dibincangkan. Perbincangan tentang *MDI* telah diskopkan dan menyebabkan cadangan untuk pengubahsuaian telah dibuat. Kesan rekabentuk nozel pada ciri-ciri semburan telah dibincangkan. Ciri-ciri semburan telah disiasat melalui pengajian kualitatif dan kuantitatif tentang masa penerbangan titisan melalui video kamera berhalaju tinggi. Keputusan eksperimen terkini tentang ciri-ciri semburan telah dibincangkan. Keputusan menunjukkan bentuk semburan pada jarak masa yang berbeza. Penggunaan daya elektrik menyebabkan semburan dimanipulasikan untuk *atomization* dan pemendapan titisan di dalam mulut dengan baik, yang mana akan menjurus kepada rekabentuk baru penyembur nasal perubatan juga turut dibincangkan.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF NOMENCLATURE

Symbol	Description	Unit
d	Diameter	μm
P	Power	Watt
l	Distance	m
σ	Electrical conductivity	S/m

LIST OF ABBREVIATION

Abbreviation	Description
MDI	Metered Dose Inhaler
DPI	Dry Powder Inhaler
CFC	Chlorofluorocarbon
SMD	Sauter Mean Diameter
pMDI	Pressurized Metered Dose Inhaler
PDA	Phase Doppler Analysis / Particle Dynamics Analysis
PIV	Particle Image Velocimetry

CHAPTER 1 INTRODUCTION

1.1 Introduction

The concept of inhalation therapy is not new. For more than a century, patients were advised to smoke cigarettes containing the anti cholinergic botanical, *Datura Stratuonium* to treat acute asthma (Crompton, 1986). The use of steam inhalation is well described in ancient medical literature and is still used as a home remedy for respiratory tract conditions (Ophir et al., 1988). The first pressurized aerosol inhaler was introduced in 1950s. One of the first clinical trials was published in 1956, using a pressurized inhaler called Medihaler (Riker Laboratories, 1956). Since their introduction, MDIs have become a cornerstone in the management of asthma, with their production exceeding 300 million units per year (Richards, 1995).

Nowadays, many different devices are used as a respiratory drug delivery system for treating asthma. Asthma can be classified as chronic respiratory diseases instead of other respiratory diseases such as bronchitis and diseases related to it. The applications of the drugs by way of inhaled aerosols are used as a route for treating a variety of respiratory diseases. In order for an inhalation device to be effective, the inhaled aerosol should reach the targeted area in the lungs.

The treatment of acute and chronic respiratory diseases such as asthma by targeting specific areas of the respiratory tract where the infection lodges would yield drug delivery directly to the site of action (Tang and Gomez, 1994). Therefore, the dosage required to achieve an adequate response could be minimized. For this reason, understanding of flow dynamics and deposition of the inhaled aerosols in the thoracic region is important in designing effective inhalation devices (Grgic et al., 2003).

There are many new design of medical nasal sprayer for treating asthma, from conventional pressurized metered-dose inhalers (MDI) to dry powdered inhaler. By looking through the conventional design of MDIs, there are many weaknesses that can be observed such as the needs of good hand and mouth coordination. There is often poor synchronization between actuation and inhalation (i.e. "hand to lung coordination") especially in elderly and pediatrics patients (Orehek et al., 1976).

Therefore, the conventional MDIs design must be improved due to this problem. Advances in science and technology and certain environmental issues have led to several modifications with respect to the technical design and the type of propellants used in MDIs. Thus, this research project will lead to a feasibility study for improving the conventional MDIs design that is well suited for treating asthma.

1.2 Introduction of Asthma

Asthma is a chronic inflammatory disorder of the airways in which many cells play a role (Rees and Price, 1995). Asthma is also known for disease of the respiratory system and around three million people in the UK, and 17 million in the USA, are asthmatic (Glaxo Wellcome, 2003). An asthma attack can cause by: -

i. Allergies
ii. Infections
iii. Exercise (too little)
iv. Change in weather

As described by Rees and Price (1995), the muscles wrapped around the airways are loose and relaxed and the airways lining is very thin. Therefore, air can easily get in and out of the sacs (i.e. alveoli) that make up the lungs. In an asthma attack, the muscles tighten up (i.e. spasm) and the airways lining swells and clogs with thick mucous. Thus, the airways become narrower and it is harder to get air in and out of the alveoli (Glaxo Wellcome, 2003). Figure 1.1 shows the lung diagram.

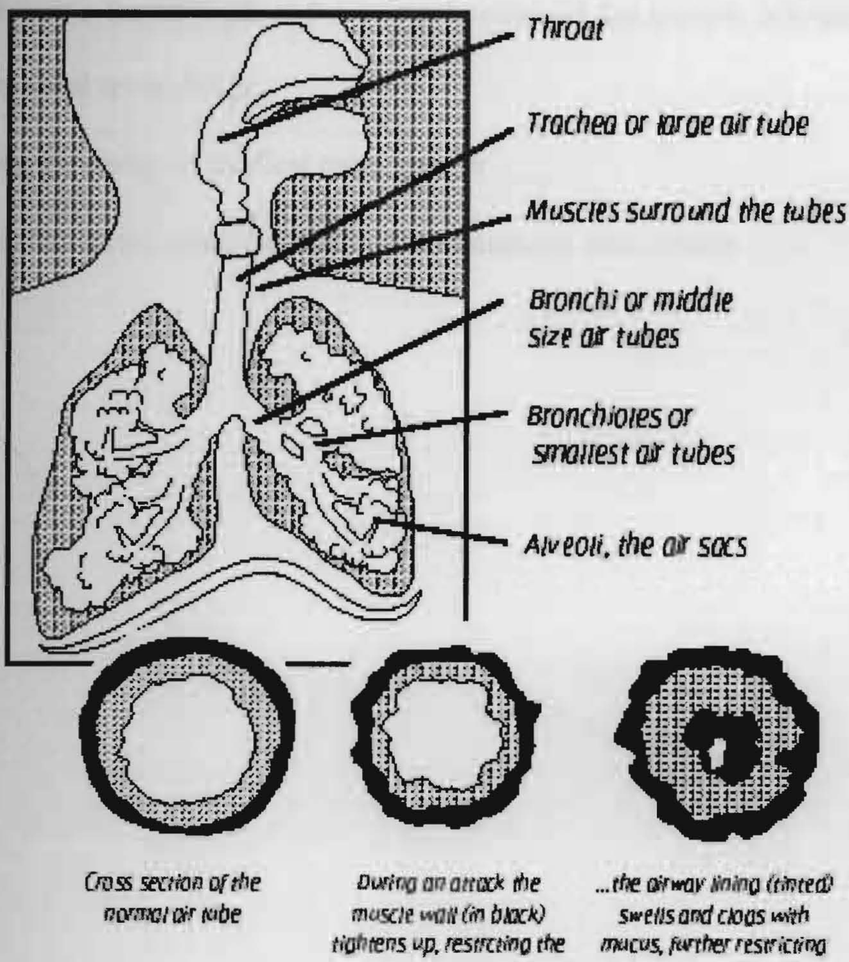

Figure 1.1 The Lungs Diagram (Glaxo Wellcome, 2003)

1.3 Objectives of the study

The objectives of this research project are: -

i. To review medical nasal sprayer.

ii. To determine the strength and / or weaknesses of the present conventional medical nasal spray design.

iii. To study the design of medical nasal sprayer.

iv. To study the initial spray characteristics of metered dose inhaler.

CHAPTER 2 LITERATURE REVIEW

2.1 Introduction

Different medicines are used to treat asthma. Some are swallowed, some are injected and some are inhaled through mouth or nose. Inhaled medicines work most quickly, because they go directly to the lungs and do not have too many side effects (Rees and Price, 1995). Thus, there are various devices that have been developed to deliver drugs competently and easy to use. However, there are three different types of inhalers, such as: -

i. Conventional metered dose inhalers (MDI)
ii. Nebuliser
iii. Dry powder inhaler (DPI)

2.2 Metered Dose Inhaler (MDI)

Inhalers deliver the drug directly to the airways. A MDI, if properly used, deposits about 10% of the drug into the airways below the larynx (Rees and Price, 1995). However, the 10% of the deposition is sufficiently enough to treat asthma (Ong, 2004). The important point in using MDI is the technique of using it. A MDI needs to be shaken and then sprayed into the mouth. Figure 2.1 shows a picture of conventional metered dose inhaler.

Figure 2.1 Conventional Metered dose Inhaler (Smith, 1995)

2.2.1 Advantages

Although the MDI is the oldest technology, it exhibits greater respirable dose in vitro and less variability in dose delivered than the newer dry powder inhaler (DPI) devices (Feddah et al., 2000). In addition, MDI have been in the market for a long time and is cost effective, that it is cheaper.

2.2.2 Disadvantages

Although MDI is one of the main respiratory delivery systems, many problems are still associated with its usage. There is often poor synchronization between actuation and inhalation "hand and lung coordination" especially in elderly and pediatrics patients (Orehek et al., 1978), lending to a failure to continue inhaling when the propellant spray hits the back of the throat (Jacqueline, 2004). However, a respiratory spacer device eliminate the need for coordination of actuation and inspiration and reduces the primary droplet size by providing extra time for complete evaporation and reduces the velocity of the aerosol particles passing through the device (Moren, 1978). A quarter of patients also have a difficulty in using a metered dose inhaler and the problem increase with age (Rees and Price, 1995). There are also concerns about the effect of CFC on the ozone layer and the environment resulting in restrictions on the continued production of CFC aerosol formulations throughout the world (Leach, 1995).

2.3 Nebulisers

Nebulisers can be driven by compressed gas (jet nebuliser) or an ultrasonically vibrating crystal (ultrasonic nebuliser). It also offers a convenient way of delivering a higher dose to the airways (Rees and Price, 1995). The delivery of the drugs depends on the type of nebuliser chamber, the flow rate and volume in the chamber. The problem that associated with nebulisers is some chambers have a reservoir and valve system to reduce the loss to the surrounding room during expiration. However, nebulisers do not use Freons and can be used to deliver aqueous solution of medications, but they are cumbersome, required longer time for drug delivery, and are not as portable as metered dose inhalers (Balmes et al., 1991). They are also expensive, often unavailable when needed, deliver variable doses and need a power supply for operation (Vaswani et al., 1998). Figure 2.2 shows a children-using nebuliser.

Figure 2.2 Child Using Nebuliser (Rees and Price, 1995)

2.4 Dry Powder Inhaler (DPI)

Another alternative to MDIs that is gaining popularity is a dry powder inhaler (DPI) (Rees and Price, 1995). As the name indicates, DPIs contains drug without propellants. In addition DPIs are breath activated so that drug particles delivered to the lung from the device depend on the aspiratory efforts of the patient (Feddah et al., 2000). So, this effort will determine the degree of emitted dose and hence non-breathing coordination with actuation is needed with these formulations.

Table 2.1 Contrasting Features of Conventional Pressurized Metered Dose Inhaler and Dry Powder Inhaler

Metered Dose Inhaler (MDI)	Dry Powder Inhaler (DPI)
1) Aerosol generation dependent on propellants (mostly Freon).	1) Aerosol generation does not require any propellants.
2) Require coordination of actuation with inhalation.	2) Relatively easy to administer since it is breath activated.
3) With correct technique the lung deposition of the drug is 10%-15%.	3) Lung deposition of the drug is similar to properly used MDI.
4) With add-on spacer device improve drug deposition into the lungs and reduced oropharyngeal side effects.	4) No add on spacer device.
5) No effect from humidity.	5) High humidity conditions may result in dumping of the powder particles (in some DPIs), resulting in a decreased respirable dose.
6) Can be used in incubated patients on mechanical ventilator.	6) Cannot be used in incubated patients.
7) Because of Freon and other additives, patients "feel" the drug delivered.	7) Some DPIs have pure drug without any additives or propellants, hence, patients may "not feel" the drug delivered and may be uncertain of the drug dosing.
8) "Cold Freon effect" causing paradoxical bronchospasm.	8) No Freon. Available in pure drug form.
9) Propellant driven aerosolized drug therefore not wholly dependent on inspiratory flow rate.	9) Drug powder release dependent on inspiratory flow rate.
10) No dose indicators. Risk of continued use of empty inhaler.	10) Newer multidose DPIs have a window with dose indicator.

There are two types of DPIs introduced more than a decade ago, namely Rotahaler by capsule, each unit of drug will be dispensed. This makes these devices inconvenient to use because it is necessary to load a capsule into the device prior to each usage. Therefore, this may create difficulty for patients with limited vision, hand tremor or arthritis. Thus, studies of ease of use of three different inhaler devices (Rotohaler, Autohaler and Conventional MDIs) in 48 arthritic patients have been studied. As a result, problem cited by these patients included failure to incorporate the twisting motion with the Rotahaler, inadequate priming of Autohaler and improper positioning of MDI (Arthur et al., 1992). To encounter these problems, two novel multi-dose inhaler devices were introduced in Europe, namely Turbuhaler by Astra Zeneca and Accuhaler / Diskus by Glaxo Wellcome. The design of Turbuhaler and Accuhaler will be discussed in the next two-sub section.

2.4.1 Turbuhaler

Turbuhaler is a multidose dry powder inhaler similar to the conventional MDI, containing 200-metered doses of the drug (Wetterlin, 2000). Unlike MDIs and other DPIs it does not contain any propellants, carriers, additives or lubricants. The inhaler device assembly consists of molded plastics and a steel spring. It has two compartments, a chamber within which the dry powder is delivered (Vaswani et al., 1998). Simple twisting the turning grip back and forth once performs the dosing. As the patients inhale through the mouthpiece, the drug is forced through small conical holes of dosing unit into the inhalation channel. A spiral insert fitted inside the mouthpiece generates high airflow resistance and disaggregates the powder to create an aerosol of small particles (Vaswani et al., 1998). Figure 2.3 shows the technical design of a Turbuhaler.

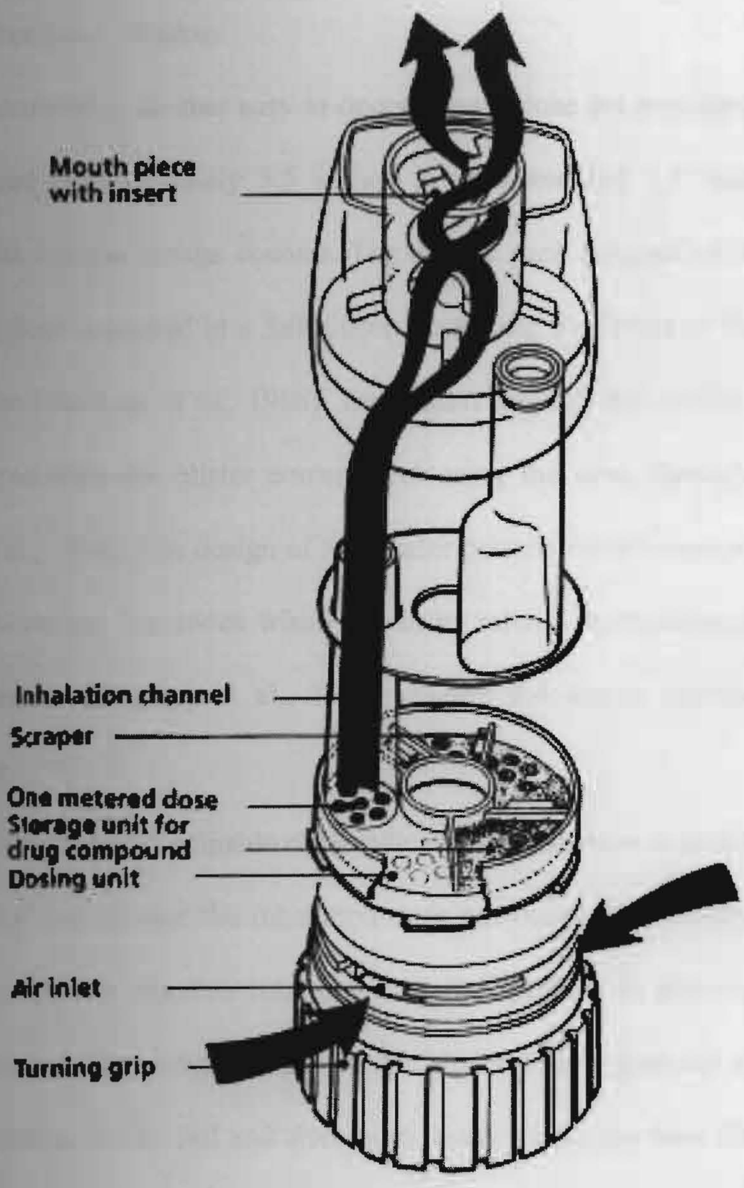

Figure 2.3 Turbuhaler Technical Designs (Vilsvik et al., 1993)

Besides, the spiral insert also increases resistance to minimize the generation of very high aspiratory flow rates. This reduces the likelihood of drug particles impinging on the posterior oropharyngeal wall (Vilsvik et al., 1993).

2.4.2 Accuhaler / Diskus

Accuhaler is another easy-to-operate, multidose dry powder inhaler. It is a pocket-sized (approximately 3.5 inches in diameter and 1.5 inches high) plastic device with built-in dosage counter. The dosage pack consists of 60-metered doses. Each unit dose is packed in a foil blister containing a mixture of dry powdered drug and lactose (Vaswani et al., 1998). Inspiration through the device draws in the air, which aerosolizes the blister contents releasing the drug through the mouthpiece (Prime et al., 1996). The design of Accuhaler permits reliable operation of the device in any orientation. The index wheel driven by ratchet mechanism aligns each blister foil accurately (Brindley et al., 1995). Figure 2.4 shows technical design of an Accuhaler.

An audible and palpable click indicates that the dose is loaded and the inhaler is ready for use. In case the inhalation does not occur after loading the device, the base foil collection chamber retains the residual powder to prevent the device from malfunctioning. The drug powder in the blister foil is guarded from moisture by sealing together the lid foil and aluminum layers within the base (Brindley, A. et al., 1995). An integral cover protects the mouthpiece.

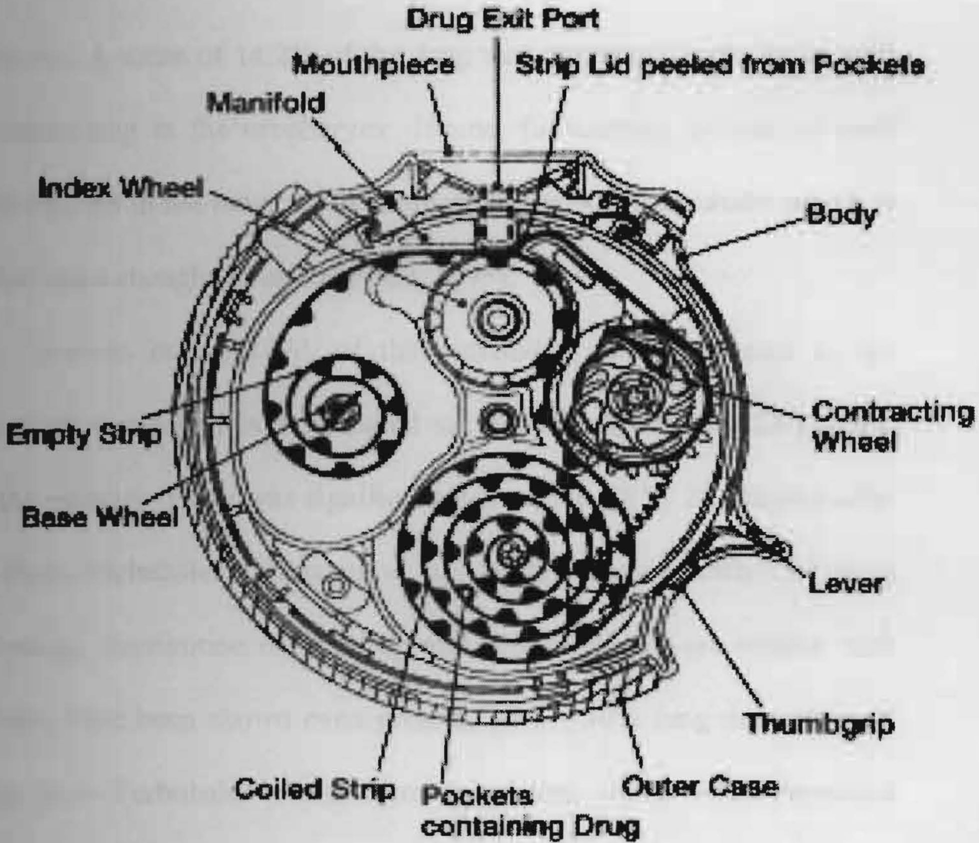

Figure 2.4 Accuhaler Technical Designs (Boulet et al., 1995)

2.5 Aerosol Drug Deposition and Distribution

Aerosol deposition is a process that caused inspired particles to be caught in the respiratory tract and thus fails to exit with expired air (Ahmed, 1990; Brain et al., 1989). Therefore, an understanding of the transport of aerosol in human lung is an important issue whether the aerosol results from atmospheric pollution, occupational factors or respiratory therapy (Lawrence and Patterson, 1990).

Previous research on extra thoracic aerosol deposition has focused largely on nasal deposition in occupational and environmental hygiene (Grgic, 2003). However, the mouth is the normal inhalation route for most therapeutic aerosols cause of its lower aerosol deposition compared to the nasal route (Grgic, 2003). Newman et al., 1990, studied the deposition and clinical effcicacy of terbutaline from Turbuhaler in 10 asthmatic patients. A mean of 14.2% of the drug was deposited in the lungs with 71.6% of dose remaining in the oropharynx. Hence, for treating asthma, at least >10% of drugs deposited in the lung, and what more to say like Turbuhaler which is 14.2%, so it is sufficient enough (Rees and Price, 1995).

Back to Newman et al., 1990, of the remainder, 13.7% adhered to the mouthpiece and 0.5% was found in the exhaled air. Therefore, bronchodilation was achieved in all the patients. There was significant increase in FEV_1 20 minutes after the inhalation from Turbuhaler (Vaswani et al., 1998). Hence, effect of drug deposition percentage, distribution of the drug and bronchodilator are similar with MDI. Other studies have been shown even greater, 20% - 30% lung deposition of aerosolized drug from Turbuhaler whilst from Accuhaler >60% drugs deposited (Borgstrom et al., 1992). In addition, Accuhaler contains micronized flixotide with at least 85% of particles of respirable size of d=5μm (Glaxo Wellcome, 2003). Beside that, the pulmonary deposition of terbutaline was approximately 8% with MDI versus 20% with turbohaler. Thorsson et al., 1994, studied the deposition of budesonide delivered through the Turbuhaler. An average of 32% drug was deposited in the airways. At an aspiratory flow rate 50 L/min, approximately 50% of the drug powder particles are <5μm in diameter (Vaswani et al., 1998).

2.5 Effect of flow rate

The inhalation flow rate is important parameters in drug delivery to the respiratory tract, because it influences the actual dose delivered to the lungs. Furthermore, the aspiratory flow often varies between individuals and between doses and is influenced by the device employed (Engel et al., 1990). The resistance of the inhalation device controls the flow inside the device and hence the amount of effort required to generate the aerosol particles (Boer et al., 1996). As a consequence, different flow in each device occurs between individual's patients and within individual patients during the course of their disease. In addition, particles intended to be delivered to the lung by inhalation should have aerodynamic diameter smaller than 5μm to increase the probability of penetrating deep into the lung and to facilitate the therapeutic activity of the drug (Feddah, 2000). Figure 2.5 shows the drug particles.

Interestingly, the increasing flow during inhalation with Turbuhaler resulted in better deaggregation of the drug particles and higher yields of terbutaline from the device. For turbuhaler, it impossible to generate inhaled flow of greater than 100L/min with it spiral channels in the mouthpiece. However, better deaggration of the drug particles at a high flow results in improved distribution and offsets the former effect (Engel et al., 1992).

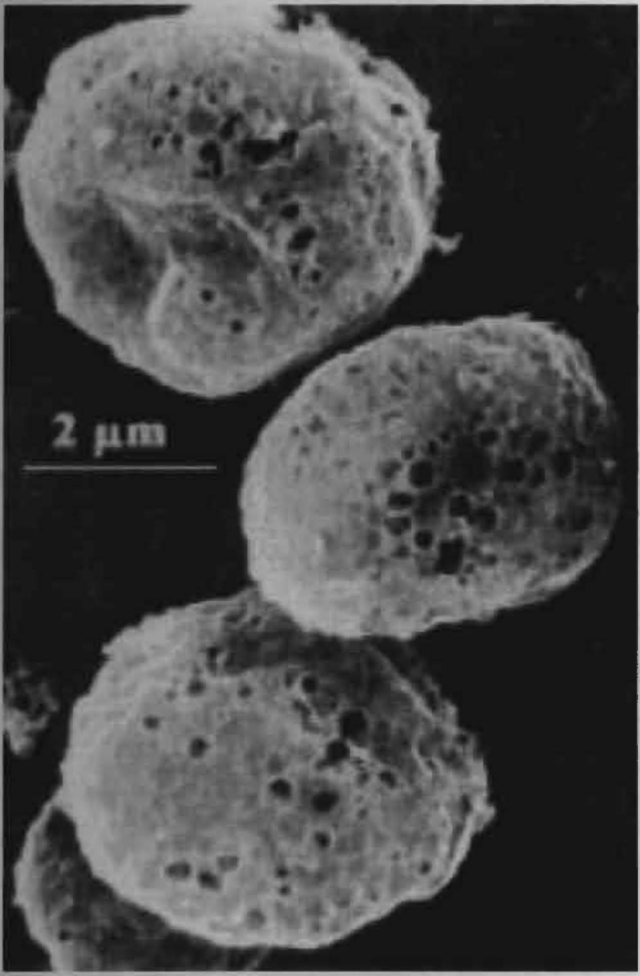

Figure 2.5 Drug Particles with a Highly Micro-porous Structure (Smith, 1995)

Unfortunately, in vitro studies suggest that the Accuhaler / Diskus is more consistent in the dose delivered at different flow rates (Prime et al., 1999), although it has a reduced fine particle mass and emits more large particles than the Turbuhaler (Barry et al., 2003). Table 2.1 shows comparison of Sauter Mean Diameter (SMD) between Accuhaler and Turbuhaler.

Table 2.1 Accuhaler Delivers Consistent Drug Doses at Low to High Flow Rates (Prime and Petchey et al., 1996)

DOSE DELIVERED EX DEVICE (% LABEL CLAIM)		
Air flow rate (l/min)	Accuhaler (SMD)	Turbuhaler (SMD)
30	87(2.9)	40(15)
60	90(4.0)	46(15)
90	92(3.3)	58(14)

CHAPTER 3 METHODOLOGY

3.1 Data Collection

3.1.1 Design of Study

One of the objectives of this research project is to determine the strengths and weaknesses of the conventional medical nasal sprayer. The method used for gaining the data is via questionnaire and interview. The questionnaire has been identified to be suitable method in collecting data for this research because it offers convenience research environment to the correspondents and eases the respondents in giving desired information logically and accurately. The population for the sample design is taken from the asthmatic patients for all range of ages, from pediatrics to elderly. Convenient sampling is used in this research because the chosen populations are conveniently available.

3.1.2 Data Collection Procedure

In obtaining the data, the researcher used e-mail and face-to-face communication in distributing the questionnaire. Fortunately, the sending process was easy because most of the targeted population have e-mail. However, it took quite some time in getting back the answered questionnaire. The user had to send out the reminder to answer and e-mail back the questionnaire as soon as possible. Not all of the targeted population returns back the questionnaire, due to invalid e-mail address and the users are being busy all the time. In analyzing the data, the researcher uses Microsoft Excel. The types of analysis are frequency and the percentage.

3.1.3 Questionnaire

The questionnaire was distributed to asthmatic patients at Normah Medical Specialist Center. Purposes of this questionnaire are to know age, gender, severity, type of medication, type of inhaler (if any) and the effectiveness of the design. Sample of the questionnaire was as below: -

Age: ______________

Gender: ______________

1) How long do you have asthma? ______________________________

2) How severe is your asthma? ______________________________

   (Mild, moderate or chronic).

3) What type of medication that you used? ________________________

   (Pills, injection or inhaler).

   *If your answer would be inhaler, please answer the question below.

   - How long have you been using inhaler? __________________
   - What type of inhaler do you use now? ___________________

     (Metered dose inhaler, dry powder inhaler or others).

4) Are you satisfied with the conventional design?

   If yes, do not proceed to the next question, but if no, why?

   ____

5) If you were given opportunities to redesign the conventional metered dose inhaler, which part would you like to justify?

   ____

   (You may answer more than 1 part)

3.2 Experimental Work

The objective of the experimental work is to observe the shape of spray plumes of metered dose inhaler (MDI). An experiment has to be conducted in order to observe the shape of spray plume in term of drugs deposition in three different types of inhaler with constant flow rate.

3.2.1 Instruments

The apparatus included a conventional metered dose inhaler. However, high-speed digital video camera was not available to capture the image photographically. At present, photography is one of the most accurate and inexpensive techniques for the measurement of drop sizes and velocities in spray. It usually in involves taking a photograph with a light pulse of sufficient intensity and sufficiently short duration to produce sharp image. The images counting and sizing were done on the processed film. Mercury vapor lamps, electrical spark, flashlights and laser pulses are widely used to create high intensity light source of short duration. High-speed photography can also be used to obtain information on drop velocities. If two light pulses are generated in rapid succession, a double image is obtained of a single drop on the photographic plate, from which measuring the distance traveled by the drop and dividing it by the time interval between the two pulses can determine the velocity of the drop.

3.2.2 Description of Apparatus

Figure 3.1 shows the arrangement of the apparatus. The high-speed camera is placed in front of the light pulses with a certain distance, l. Therefore, the delivery device, which is inhaler is placed between the camera and the light pulse. Since researcher could not use laser as the light pulse, thus, researcher uses a high power light source, which is 100W.

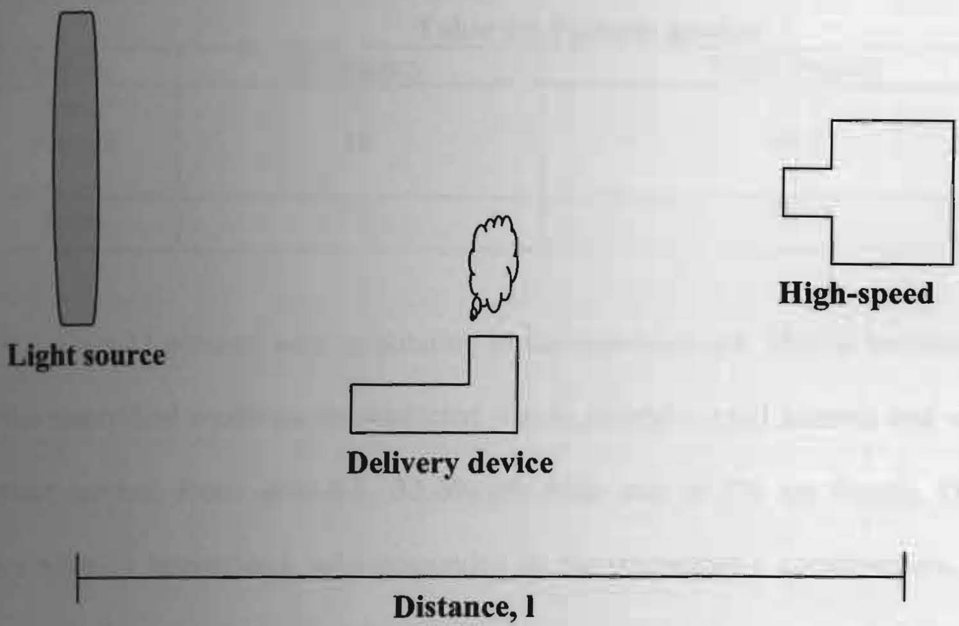

Figure 3.1 Arrangement of the Apparatus

Switching on the light source and the high-speed camera continuously as shown in figure 3.1 captured the images. The inhaler pressed while the camera was like in the figure above. Therefore, the high-speed camera will capture the images in order for the researcher to comment on the shape of spray plumes. This method is quite straightforward because the purpose of this experiment is to observe the shape of spray plumes, while the light pulse acts as a very short duration freezing the motion of the fast moving objects. In analyzing the data, researcher observes the shape of spray plumes images of the conventional metered dose inhaler.

CHAPTER 4 RESULTS AND DISCUSSION

4.1 Questionnaire

The questionnaire has been distributed to 20 people, 10 male and 10 female asthmatic patients. Table 4.1 shows the patient's gender.

Table 4.1 Patients gender

Gender	Frequency	Valid Percent
Male Female	5 10	33.3 66.7
Total	15	100.0

Only 15 patients were responding to the questionnaire. This is because some of the respondent could not be contacted due to invalid e-mail address and without contact number. From table 4.1, 33.3% are male and 66.7% are female. Overall, there were 15 respondents, who responded to the researcher's questionnaire. Table 4.2 shows the patient's age by majority.

From table 4.2, 26.7% were 30 years old, 33.3% were 45 years old and 40% were 60 years old. Therefore, the researcher concluded that most of the patients are older generation. This may be due to lack of exercises, foods consumption and other factors.

Table 4.2 Patients Age

Age	Frequency	Percent
30	4	26.7
45	5	33.3
60	6	40.0
Total	15	100

From table 4.3, it shows that 20% of the patients have mild asthma, 53.3% were at a moderate stage and 26.7% were at a chronic stage. At different stage of severity, the asthmatic patients will treated by different types of dosages (Ong, 2004). For example, at a moderate stage, the patients use 100 micrograms of the drugs with 200-metered actuations.

Table 4.3 Patients Severity

Severity	Frequency	Percent
Mild	3	20
Moderate	8	53.3
Chronic	4	26.7
Total	15	100

However, in table 4.4, it shows a table for types of medication that been used for asthmatic patients. These include pills, injection and inhaler. 26.7% patients were using pills, 13.3% using injection and 60% patients were using inhaler. This means majority of the patients used inhaler as their medication method because it was easy to use, more effective and easy to get. However, it is still depend on how severe is the asthma. From the table 4.4, researcher can determine what type of inhaler that been used by the asthmatic patients, such as, 66.7% patients used metered dose inhaler, 13.3% used dry powder inhaler and 20% used other types. Therefore, researcher concludes that majority of the asthmatic patients using metered dose inhaler as compare to dry powder inhaler or other types. This is because metered dose inhaler is cheaper than the dry powder inhaler.

Table 4.4 Types of Medication

Types of Medication	Frequency	Percent
Pills	4	26.7
Injection	2	13.3
Inhaler	9	60
Total	15	100

Researcher also found that 80% patients were satisfied with the conventional design whereas 20% patients were not satisfied with the design. Most of the patients that were not satisfied with the design were the elderly people. This because they were not capable to press the canister due to arthritic and this leads to poor hand and mouth coordination. Hence, a slight modification of the design is needed especially for the arthritic patients.

4.2 Experimental Work

4.2.1 Criteria for Spray Plume Characteristics

Sprays may be produced in many ways. Normally, high relative velocity between the liquid to be atomized and the surrounding air or gas is needed. Therefore, there are many types of atomizers that are available and their selection is based on their applications. Hence for a pressurized metered dose inhaler (pMDI) it used pressure atomizer types. As their name suggests, pressure atomizers rely on the conversion of pressure into kinetic energy to achieve high relative velocity between the liquid and the surrounding air or gas. Most of the atomizers in general use are of this type. They include plain orifice and simplex nozzles, as well as various wide range designs such as variable geometry, duplex and dual orifice injectors. Hence, for pressurized metered dose inhalers, most of it used plain orifice nozzle type.

However, we also need to know the requirements for an atomizer. As stated by Lefebvre (1989), an ideal atomizer would possess all the following characteristics:

i. Ability to provide good atomization over a wide range of liquid flow rates.
ii. Rapid response to changes in liquid flow rates.
iii. Freedom from flow instabilities.

iv. Low power requirements.

v. Capability for scaling, to provide design flexibility.

vi. Low cost, lightweight, ease of maintenance and ease of removal for servicing.

vii. Low susceptibility to damage during manufacture and installation.

4.2.2 Atomization Characteristics for a Plain Orifice

The atomization of a low viscosity liquid is most easily accomplished by passing it through a small circular hole. If the velocity is low, the liquid emerges as a thin distorted pencil, but if the liquid pressure exceeds the ambient gas pressure by about 150kPa, a high velocity jet is formed that rapidly disintegrates into a well-atomized spray. According to Lefebvre (1989), disintegration of the jet is promoted by an increase in flow velocity, which increases both the level of turbulence in the liquid jet and the aerodynamic drag forces exerted by the surrounding medium, and is opposed by increases in surface tension and liquid viscosity, which resist breakup of the ligaments.

Moreover, as described by Lefebvre (1989), the sprays produced by plain orifice atomizers have a cone angle that usually lies between 5° and 15°. This cone angle is only slightly affected by the diameter and length per diameter ratio of the orifice and is mainly dependent on the viscosity and surface tension of the liquid and the turbulence of the issuing jet. An increase in turbulence increases the ratio of the radial to the axial component of velocity in the jet and thereby increases the cone angle. Hence, this characteristic is very important in determining the drug in the metered dose inhaler spreads through out human mouth.

Thus, the characteristics of atomization for plain orifice can be best illustrated by the figure 4.1. The jet spreads out into a cone with an angle depending on the liquid velocity and the orifice size. As shown in figure 4.1, the jet splits into layer with various velocities. The center of the spray has the highest velocities. The center layers affect the velocities of the outer layers. Therefore, the outermost layers have the lowest velocity and the inner layers have highest velocity. Small waves occur in each layer. The surface of each layer breaks into ligament due to interactions among drag, surface tension and viscous forces. While, ligaments in (4) break further, until they are stable, normally in a spherical geometry. Whereas, drops in (5), break further into more stable drops. Finally, drops coalesce.

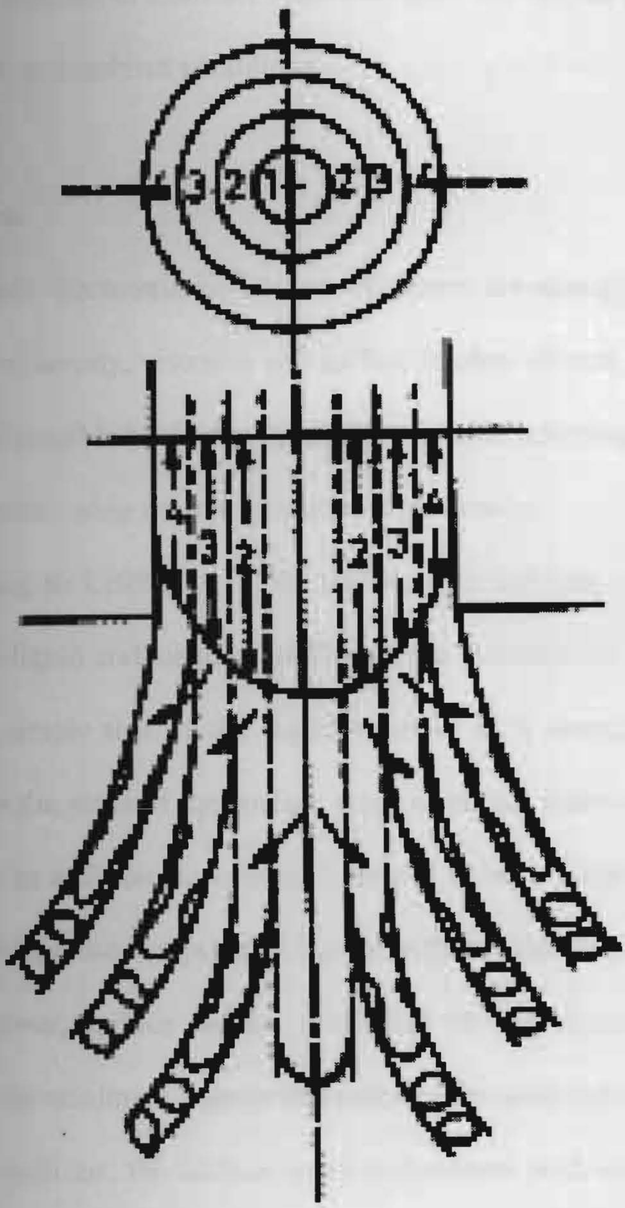

Figure 4.1 Mechanism of Jet Atomization for a Plain Orifice (Elkobt, 1982)

4.2.3 Factors Influencing Atomization

Performance of any type of atomizer depends on its size and geometry and on the physical properties of the dispersed phase and the continuous phase. For case of the pressurized metered dose inhalers, that used plain orifice nozzles type, the dimension most important for atomization is the diameter of the final discharge maintained constant, an increase in atomizer scale (i.e. size) will impair atomization. Such as, liquid properties and ambient conditions.

4.2.3.1 Liquid Properties

The flow and spray characteristics of most atomizers are strongly influenced by the liquid properties of density, viscosity and surface tension. Hence, as stated by Tate (1969), it is seldom possible to change the density without affecting some other liquid property, so this relationship must be interpreted cautiously.

Besides, according to Lefebvre (1989), one way of defining a spray is in terms of the increase in liquid surface area resulting from atomization. The surface area before breakup is simply that of the liquid cylinder as it emerges from the nozzle. Thus, the area is the sums of the surface areas of all the individual droplets occur after atomization. In addition, as said by Lefebvre (1989), surface tension is important in atomization because it represents the force that resists the formation of new surface area. However, surface tension multiplied by the increase in liquid surface area is equal to the minimum energy that required for atomization. For most pure liquids in contact with air, the surface tension decreases with an increase in temperature and is independent of the age of the surface (Christensen, 1980).

Moreover, in many respects, viscosity is the most important liquid property. Viscosity, its importance stems from the fact that it affects not only the drop size distributions in the spray but also the nozzle flow rate and spray pattern. Therefore, an increase in viscosity lowers the Reynolds number and also hinders the development disintegration and increases the size of the drops in the spray (Solomon, 1985).

4.2.3.2 Ambient Conditions

Sprays are injected into by ambient gas can vary widely in pressure and temperature. According to Lefebvre (1989), if the ambient pressure is raised continuously above the normal atmospheric value, the mean drop size increases initially until a maximum value is reached and then slowly declines. Hence, for plain orifice nozzle types, that are applied for pressurized metered dose inhaler, an increase in ambient gas density leads to a wider spray angle. This is because, the increase in aerodynamic drag on the droplets, created by an increase in gas density, tends to produce a greater deceleration in the axial direction than in the radial direction. As a result, in general, an increase in air density will cause the spray pattern to adhere more closely to the streamlines of the atomizing air.

4.2.4 Droplet Size Distribution

Drop size is a key factor in the performance of MDI for treating asthma. These need to deliver drug to the lungs. If the droplets are too small, the patient simply exhales the drug, while if they are too large the drops stick in the mouth and windpipe where they can cause side effects including infections. Hence, to produce more effective inhalers, combined with the requirement that the patient feel comfortable with the product, a solid understanding of the operation of the devices is needed. The smallest droplets size that has been achieved is 1.1μm in diameter (Oxford Lasers, 2003).

It was a technique where we can obtain the droplet size distribution by using particle dynamics analysis or also known as phase Doppler analysis (PDA). The most popular application is the analysis of atomized liquids (i.e. sprays). Sprays are used in countless applications, both in industrial processes and commercial products. The spray nozzle has a decisive influence on the distribution and droplet size of the atomized liquid in application such as pharmaceutical sprays, which in this research project is a metered dose inhaler (MDI). PDA approach has several advantages where as: -

i. The measurements are relatively unaffected by the random beam attenuations provided the signal-to-noise ratio is sufficient.

i. The instrument response is linear over the entire working range.

i. It has a potentially large size dynamic range. The dynamic range is limited only by the detector response and to signal-to-noise ratio (Bachalo, 1984).

Figure 4.2 shows several principles of particle dynamics analysis (PDA) such as: -

i. The measurements are performed at the intersection of two laser beams, where there is an interference fringe pattern of alternating light and dark planes (A).

i. Particles scatter the light, which appears to flash, as the particles pass through the bright planes of the interference pattern. Receiving optics placed at an off-axis location focus scattered light onto multiple detectors (B).

i. Each detector converts the optical signal into a Doppler burst with a frequency linearly proportional to the particle velocity (C).

v. The processor measures the phase difference between the Doppler signals from different detectors. This is a direct measure of the particle diameter (D).

v. The results are processed by software (E).

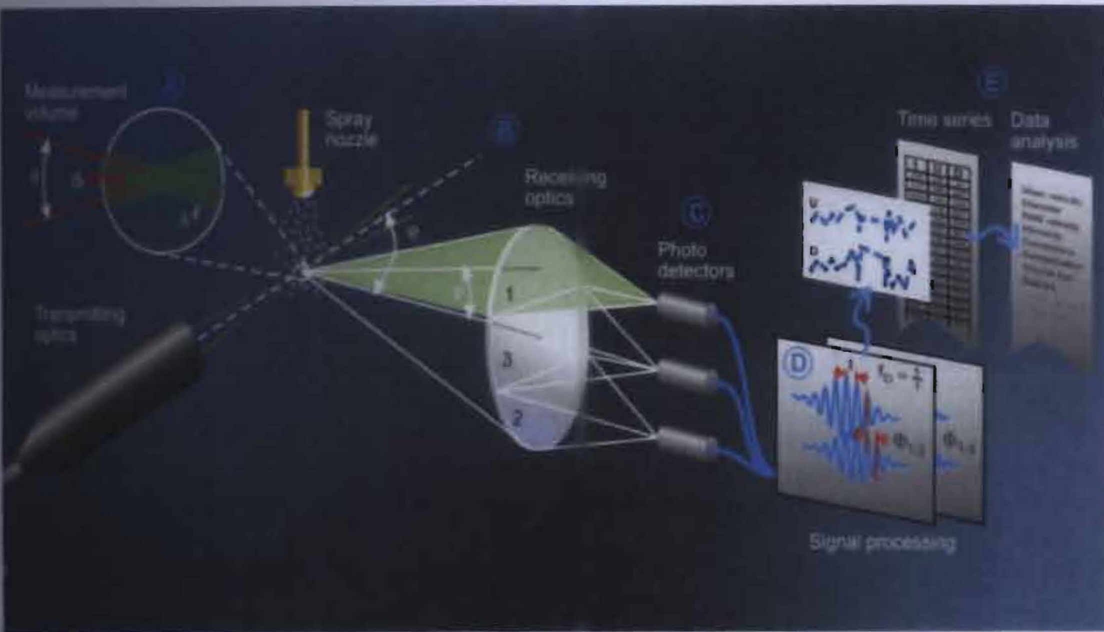

Figure 4.2 Principles of particle dynamics analysis (PDA) (Dantec Dynamics, 2004)

Figure 4.3 shows the characterization of a spray created by a metered dose inhaler (MDI). Small handheld-metered dose inhaler (MDI) can generates droplet size measurements. The ability of small aerosol droplets to be deposited in the human lung or nasal tract depends very much on the size of the droplets. The long-term temporal stability of the aerosol generation is also important.

Figure 4.3 Characterization of a spray created by metered dose inhaler (MDI) (Oxford Lasers, 2003).

4.2.5 High Speed Photography

Photography is one of the most accurate and least expensive techniques for the measurement of drop sizes and velocities in sprays. Usually, it involves taking a photograph with a light pulse of sufficient intensity and sufficiently short duration to produce a sharp image and then counting and sizing the images on the processed film. In this research project, halogen light is used to create a high-intensity light source of short duration.

Photography is probably the only technique with the potential to provide drop size information from dense, fast moving sprays of interest in power generation (Jones, 1977). However, the photographic images analysis always causes at least some degree of human involvement and manual sizing is tedious and time consuming and invariably subject to operator fatigue and bias.

High-speed camera can also be used to obtain information on drop velocities. If two light pulses are generated in rapid succession, a double image is obtained of a single drop on the photographic plate, from which the velocity of the drop can be determined by measuring the distance traveled by the drop and dividing it by the time interval between the two pulses (Lefebvre, 1989). Particle images are determined by measuring each particular diameter, and the difference between the diameters is a measure of the thickness of the blurred "halo" at the edge of the particle (Chigier, 1976). This means, the effective depth of field is determined for each particular optical system and particle size. As a conclusion, imaging systems allow the spray to be "seen", but a major difficulty is the determination of the size of the viewing volume to be assigned to given drop sizes.

4.2.5.1 Light sheet and the Elimination of Blur

Figure 4.4 below shows stills taken from a high-speed camera taken in the configuration shown in the light sheet illumination (Oxford Lasers, 2003). The sprayer is a metered dose inhaler. The images also visually observed in the study.

Figure 4.4 Metered dose inhaler spray formation (Oxford Lasers, 2003)

Therefore, to obtain the above pictures, using two types of lighting such as backlighting and light sheet illumination can do it. Hence, good understanding in laser applications were very important. Light sheet and the elimination of motion blur was work by a laser emitting very short pulses is used to illuminate the subject. The laser light acts as a very short duration strobe lamp for the camera, freezing the motion of fast moving objects and removing any motion blur. Three lasers offered emit 1μs, 30ns or 10ns pulses in perfect synchronization with the high-speed camera.

There are two types of lighting are possible such as light sheet illumination and backlighting. Figure 4.5 shows light sheet illumination whereas figure 4.6 shows backlighting. For light sheet illumination, the light can be shaped into a 2 dimensional light sheet. This is used to take slices through the 3-dimensional spray, dissecting the subject, to reveal the flow patterns. This is illustrated right. If two images are taken in quick succession, the slight differences between them can be measured by special software. This technique, known as Particle Image Velocimetry (PIV) gives rise to a map of velocity against position over the whole subject.

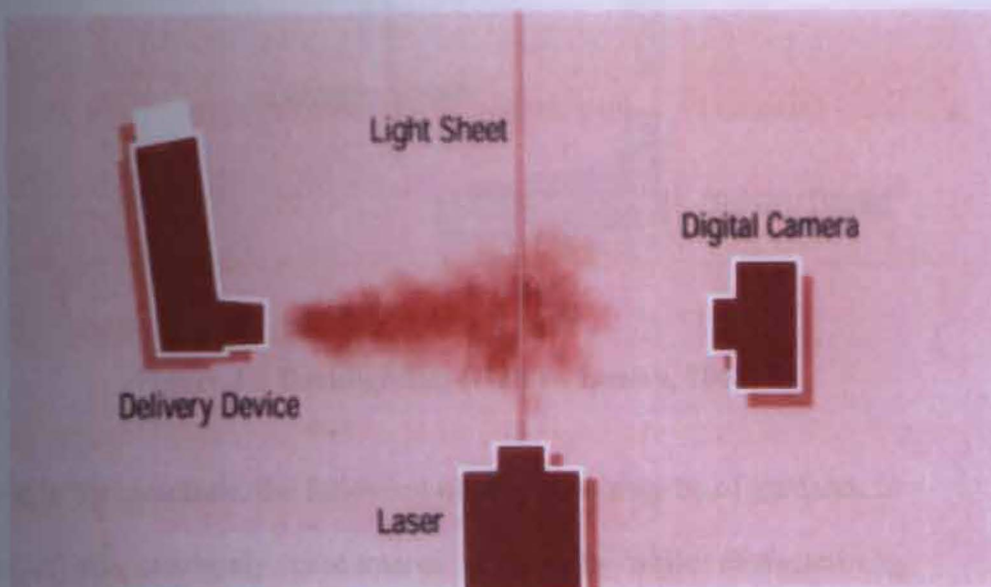

Figure 4.5 Light sheet illumination (Oxford Lasers, 2003)

However, for backlighting technique, the light can diffuse by a screen behind the subject. This allows accurate size and shape measurements. The laser light can deliver by fiber optics and endoscopes to allow illumination of subjects normally inaccessible to standard light-sources. Laser light can be focused to a very small area and this is can be useful when using high-magnification lenses to image very small areas. This can image droplets with diameter, d as small as $1\,\mu m$.

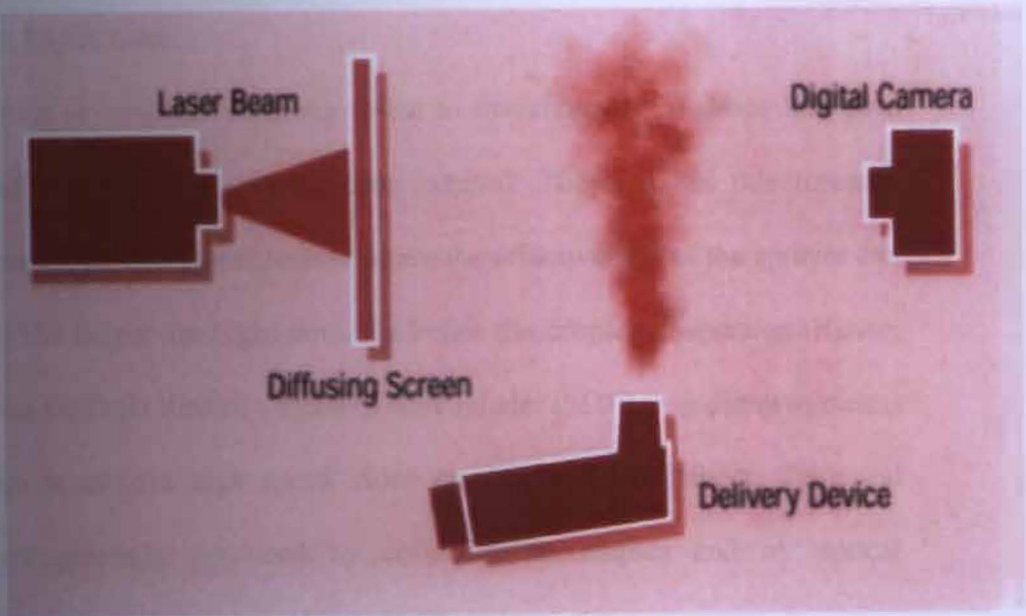

Figure 4.6 Backlighting (Oxford Lasers, 2003)

However, in the meantime, the following observations may be of guidance in avoiding some of the commonly encountered drawbacks while characterizing available methods of drop size distribution in sprays, such as: -

i. No single parameter can completely define drop size distributions in spray.
ii. There is no universal correlation between the mean diameter of a spray and its drop size distribution. They are completely independent of each other.
iii. Relative span factor can be used to indicate the spread of drop sizes in a spray.
iv. Dispersion boundary factor can be used to define a meaningful maximum drop size.

4.2.5.2 Droplet Flight Time

Flight time or temporal sampling refers to measurement of drops that pass through a fixed area during a specific time interval. Therefore, in this research project, flight time is an important element where the effectiveness of the sprayer can be determined. The longer the flight time, the better the droplets dispersion. Hence, in order to obtain the flight time of a metered dose inhaler (MDI), a qualitative means involved, which is using a high speed video camera and laser sheet. Temporal distributions are generally produced by collection techniques and by optical instruments, which are capable of sensing individual drops. With pressure atomizers, the smaller drops in the spray usually decelerate more rapidly than the larger drops, which lead to a high concentration of small drops just downstream of the atomizer.

As we refer to figure 4.4, the shape of spray plumes kind of like misty shape. At difference time intervals, the plumes were become like a cloudy shape. This only can be obtained if we spray a conventional MDI. Finally, as a conclusion, if an electrostatic charged were applied for MDI application, it will give a great advantage for inhalation. Electrostatic forces can be used to deflect charged drop trajectories, so that drop deposition onto a target can be controlled. This because since conventional inhaler was in misty forms, the drugs distribution will be dispersed in the human trachea in a short period of time before it reaches the targeted area, which is the lung. As compare to an electrically charged MDI, the dispersion of the drugs will be charged at the trachea lining until it reaches the lung without wastage.

4.3 A Novel Electospray Metered Dose Inhaler

An electrically charged spray has the benefits of lack of droplet agglomeration, low droplet concentration, controllable droplet size distribution, controllable spray plume shape and controllable droplet deposition (Law, 2001). The advancement in laser and photographic methods on the other hand has enabled the spray characteristics to be studied qualitative and quantitatively. Electro atomization is a new technique able to produce monodisperse droplets of a defined size in the micrometer range. It is based on techniques that are new to the field of medical atomization, and, although the system is still in its infancy, it seems a promising technique because of its potential to be converted into small hand-held devices. Figure 4.7 shows an experimental setup for electrospray metered dose inhaler. Monodisperse aerosols show therapeutic advantages, but they are difficult to generate. A new method (electro atomization) is described. A high voltage is applied to a nozzle through which a solution, containing dissolved drug, is pumped. At the nozzle tip, a liquid cone is formed and a stream of monodisperse droplets is released.

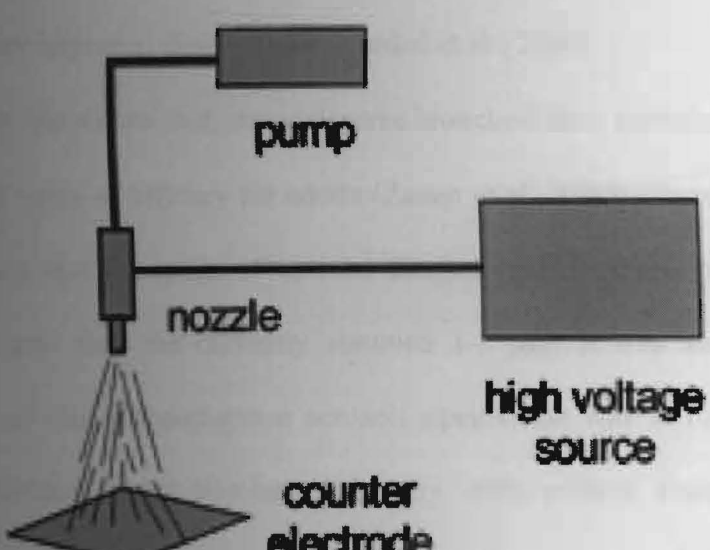

Figure 4.7 Electrospray metered dose inhaler (Ijsebaert et al, 2001)

The density, conductivity, and the flow rate of the fluid govern the droplet diameter. The use of conventional inhalation devices, only a fraction of the inhaled drug reaches the lower airways, where it has its therapeutic effect (Biddiscombe et al., 1993). Liquids with a high surface tension (i.e. pure water) are hard to spray: high nozzle voltages are needed so that the breakdown threshold of the surrounding gas is passed easily. If the liquid flow rate is too low, no stable cone can be formed. At increasing flow rates, more liquid leaves the cone, and the electric charges needed for a particular cone shape become insufficient. The cone shape cannot be maintained, and a new equilibrium will be found with a larger jet diameter (i.e. larger droplets). The droplets produced have a high charge and need to be neutralized. Because of evaporation, droplets shrink, and the charge in the droplets increases, were causing uncontrollable disruption. A direct-current corona discharge (using a sharp needle setup) can be used to discharge the droplets. A large part is deposited in the mouth and throat, after which it is swallowed and subsequently may be absorbed in the gastrointestinal tract. The low efficiency of the inhalation equipment is related to the less optimal size distribution of the particles released, although recently developed inhalers can show improved distributions (Kunkel et al., 2000).

Research has shown that, monodisperse bronchodilator particles of d=2.8μm were optimal in terms of efficacy for adults (Zanen et al., 1995). These experiments point to the fact that the range of optimal aerosol particle sizes might be much smaller (2-3.5 μm) than the currently assumed 1-5 μm. It was also shown that administration of these monodisperse aerosols opened the way to reduce the dose emitted from metered or dry powder inhalers by ~80% without losing any clinical effect (Zanen et al., 1995). Large particles are less efficacious; therefore, they may be eradicated from the emitted dose without reducing the therapeutic effect. However, they still have the potential to elicit side effects. Smaller particles are exhaled directly or deposit in the alveoli, where they are not effective due to the lack of smooth muscle. As a result of these findings, an interest in (producing) monodisperse aerosols has emerged as a means to improve the therapeutic quality (Thompson, 1998).

CHAPTER 5 CONCLUSIONS AND RECOMMENDATION

5.1 Conclusions

The spray systems used as the medical nasal sprayer were investigated. The advantages and disadvantages, and the spray characteristics of the conventional spray system were discussed. The design of metered dose inhaler has also been reviewed. The metered dose inhaler was widely used in the health application. From the observation of the shape of spray plumes, the drugs dispersion was very short for conventional MDI. Thus, the suggestion has been made in this research project. The results obtained through this study will be used to design a more efficient spray system. An electrospray of MDI also has been discussed.

5.2 Future Work

The results obtained through this study will be used to design a more efficient spray system. Future work includes an electrostatic sprayer that has the benefits of lack of droplet agglomeration, low droplet concentration, controllable droplet size distribution, controllable spray plume shape and controllable droplet deposition (Law, 2001). The application of external electrical field has enabled the spray plume to be manipulated for better droplets atomization and droplets deposition in the human airways tract. Thus, the application of other techniques such as charge injection technique (Rigit and Shrimpton, 2003) with a higher flow rate will be investigated in this study. The study will combine both experimental studies on initial spray characteristics produced from MDI. The aim of the study is to design a novel electrostatic spray system that is well suited to the health environment. A liquid is supplied to a nozzle, and an electric field is generated between the nozzle and a counter electrode. When the electrical stress overcomes the surface tension of the liquid, a cone is formed, from which a thin jet emerges. The droplet size is dependent on the liquid flow rate and the liquid properties (i.e., conductivity, surface tension, and density).

When the electrical conductivity of the liquid is too low, $\sigma=10^{-8}$-10^{-10} S/m, insufficient current can flow, and the liquid cannot be sprayed. The conductivity needs to be higher than $\sigma=10^{-6}$ S/m, but too high levels lead to an unstable spray process. In the corona region, a dense cloud of free electrons is produced, forming negative ions in the air. These discharge the positively charged droplets. Hence, the charged droplets will attracted to the trachea lining without a waste before it reaches the targeted area (i.e. lung). This will gives an electrospray great benefit in health application. From this understanding of the charged droplets under the influence of electric field, it could be concluded that the shape of charged sprays is controllable by using electric field, either by stretching or confining the spray plume. The design of a novel electrostatic MDI based on the charge injection technique is still in investigation and observation.

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